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RAPID COMMUNICATION

Pegylated-interferon alpha 2a treatment for chronic hepatitis C in patients on chronic haemodialysis

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Abstract

AIM: To evaluate the response to pegylated-interferon alpha 2a in chronic hepatitis C patients on chronic haemodialysis.

METHODS: Ten patients with chronic C hepatitis were enrolled in this study. All had increased aminotransferases for more than 6 mo, positive antiHCV antibodies and positive PCR HCV-RNA. We administrated Peg-Interferon alpha 2a 180 μg/wk for 48 wk. After 12 wk of treatment we evaluated the biochemical and early virological response (EVR). At the end of the treatment we evaluated the biochemical response and 24 wk after the end of the treatment we evaluated the sustained virological response (SVR). We monitored the side-effects during the treatment.

RESULTS: Two patients dropped out in the first 12 wk of treatment and 2 after the first 12 wk of treatment. After 12 wk of treatment, 7 out of 8 patients had biochemical response and EVR and 1 had biochemical response but persistent viremia. We had to reduce the dose of pegylated-interferon to 135 μg/wk in 2 cases. Three out of 6 (50%) patients had SVR 24 wk after the end of the treatment. Intention-to-treat analysis showed that 3 out of 10 patients (30%) had SVR. Side-effects occurred in most of the patients (flu-like syndrome, thrombocytopenia or leucopoenia), but they did not impose the discontinuation of treatment.

CONCLUSION: After 12 wk of treatment with Peg-Interferon alpha 2a (40 ku) in patients on chronic haemodialysis with chronic C hepatitis, EVR was obtained in 87.5% (7/8) of the cases. SVR was achieved in 50% of the cases (3/6 patients) that finished the 48 wk of treatment.

INTRODUCTION

Although constant efforts have been made to improve the outcome of hepatitis C patients, chronic infection with hepatitis C virus (HCV) remains a problem for hepatologists. The development of new therapeutic formulas (pegylation) and the introduction of ribavirin were major steps forward. However the problem is not entirely solved since the sustained virological response can be obtained in only half of HCV-infected patients. There are also the special groups of patients (with liver cirrhosis, with HIV coinfection, patients on chronic haemodialysis) in which the optimal antiviral treatment is still not established.

In patients on chronic haemodialysis, the number of individuals infected with HCV is rather high mostly due to nosocomial infection. The reported prevalence of HCV infection ranges from 8% to 20% in dialysis patients in developed countries[1-5] and much higher in less developed countries[6]. The prevalence of anti-HCV among dialysis patients was 43.9% in Saudi Arabia in 2001[7], 30% in India in 2002[8], and 41% in Turkey (2001)[9]. In United States of America in 2000, 8.4% of haemodialysis patients were anti-HCV positive[5]. The incidence of HCV infection is higher in patients undergoing dialysis at hospitals than in those undergoing haemodialysis or peritoneal dialysis at home.

The main mechanisms involved in nosocomial infection with HCV in haemodialysis patients are filter reuse, use of contamined haemodialysis machines and contamination of medical staff's hands[10]. It has been proven that the incidence of HCV infection in haemodialysis patients increases if the nurse does not change her gloves before injecting each patient[11] and if HCV (+) patients undergo haemodialysis in the same room with HCV (-) patients[12].

Other possible risk factors for transmission of the virus are sharing single vials to prepare drugs or infusions for different patients, distance less then one meter between chairs[13], sharing a single heparin-saline solution ampoule in different patients[14]. A large French multi-center study[15] on 1323 haemodialyzed patients has shown an incidence of 0.4% new HCV infections per year, almost two thirds of them occurring in infected patients on dialysis during the same shift at the same unit.

Regardless of the route of infection, the evolution of HCV-infected patients on chronic haemodialysis is often severe. Martin *et al*[16] showed that 24% of haemodialysis patients with positive anti-HCV Ab have liver cirrhosis and that there is no correlation between the severity of hepatic lesions and viral genotype, viral load or transaminase level. Hence we must treat chronic hepatitis C in haemodialysis patients, particularly in those on the waiting list for renal transplantation, because post-transplant immunosuppressive therapy can accelerate the natural course of the liver disease. Interferon-based therapy is not recommended in HCV positive patients after renal transplantation due to a significant risk of graft loss and a low rate of clearance of the virus[17,18]. Also ribavirin monotherapy for renal transplant recipients positive for anti-HCV is associated with improvement in liver enzymes but not significant change of HCV RNA[19]. On the other hand, Kamar *et al*[20] showed that treatment of HCV positive haemodialysis patients with interferon α could induce complete and sustained clearance of the virus in almost 29% of them, without any relapses after renal transplantation despite subsequent immunosuppressive treatment.

Another problem of the treatment for HCV-infected patients on dialysis is the contraindication of ribavirin, due to the risk of deep and long-lasting haemolytic anaemia[21].

Due to these characteristics of this special group of patients and the promising results of our previous study using standard interferon in haemodialysis patients[22], we decided to evaluate the effect of pegylated-interferon in patients with chronic hepatitis C on dialysis.

MATERIALS AND METHODS

We included 10 haemodialysis patients in our study (4 males and 6 females, mean age 40.2 years). Written informed consent to participate in this study was obtained from all of them. All had increased aminotransferases for more than 6 mo, anti-HCV antibodies (Elisa Ⅲ) and positive PCR HCV-RNA. The viral load at admission and after 12 wk of treatment (EVR) was determined by the classical polymerase chain reaction (Roche) with a detection limit of 600 UI/mL. The viral load 24 wk after the end of treatment (SVR) was determined by real-time PCR (Abbott) with a detection limit of 23 UI/mL. None of the patients presented with clinical, biological, endoscopic or ultrasound signs of liver cirrhosis. We did not perform liver biopsy because of the increased risk of bleeding in haemodialysis patients.

All patients were treated with pegylated-interferon alpha 2a (180 μg/wk) for 48 wk. We evaluated the biochemical response every month and the virological response after 12 wk of treatment (early virological response-EVR) and 24 wk after the end of treatment.

We monitored the side effects during the treatment. At the end of the treatment we evaluated the biochemical response of our patients (number of patients with normal transaminases) and the sustained virological response (SVR) 24 wk after the end of the treatment (72 wk from the beginning of the treatment) by determining the virological load.

RESULTS

The 10 patients studied are listed in Table 1. At the beginning of the study the virological load was low in 2 patients (< 10 kIU/mL), moderate in 5 patients (10-500 kIU/mL), and high in 3 patients (> 500 kIU/mL). Two patients were excluded from the study. One patient was excluded because of lack of compliance and 1 patient discontinued the treatment due to complications after surgery (sepsis).

We determined the biochemical and virological response (PCR RNA HCV) in the 8 patients who continued the treatment after 12 wk of therapy. Of these patients, 7 (87.5%) had biochemical response (normal transaminases) as well as virological response (viral load < 0.6 kIU/mL), 1 (12.5%) had biochemical response (normal transaminases) but persistent viremia. We continued the treatment with pegylated-interferon alpha 2a for 48 wk. During this period one patient died of cerebral haemorrhage caused by arterial hypertension after 16 wk of therapy (the patient having normal prothrombin time and only mild thrombocytopenia-104 000 platelets/mL) and one patient was excluded from the study due to lack of compliance after 28 wk of therapy.

The total number of patients who finished the 48-wk treatment was 6 (60%). All of them had biochemical response at the end of treatment (normal transaminases). Three out of 6 patients (50%) had sustained virological response (SVR) 24 wk after the end of the treatment. The intention-to-treat analysis showed that 3 out of 10 patients (30%) had sustained virological response 24 wk after the end of the treatment.

All patients had minor flue-like symptoms, 4 had mild thrombocytopenia (Tr < 150 000/mm^3) and 2 had moderate thrombocytopenia (Tr < 100 000/mm^3), 4 had transitory mild leucopoenia (L < 4000/mm^3). In the 6th mo of therapy one of the patients developed sepsis secondary to central venous catheter infection. During this period the patient had elevated transaminases. Unfortunately, this patient abandoned the treatment one month later.

We modified the dose of pegylated-interferon in 2 patients. In one we reduced it to 135 μg/wk for 1 mo (because of the thrombocytopenia and haemorrhagic complications-metroragia, epistaxis, prolonged bleeding of the fistula), then 180 μg/wk was administered again. In the second patient the dose reduction to 135 μg/wk was initiated in the 4th mo of therapy until the end of 48-wk treatment.

We did not stop the treatment in any patient due to severe side effects of pegylated- interferon.

Table 1 Demographic data of haemodialysis patients treated with pegylated interferon

No.	Patient	Sex	Age	Duration of treatment wk	Stop of because treatment of	Initial viral load (UI/mL)	Viral load at wk 12 (UI/mL)	Viral load at wk 72 (UI/mL)
1	B.L.	F	42	48		4090	< 600	< 23
2	C.A.	M	34	48		84 760	< 600	45
3	B.V.	M	45	48		252 000	< 600	263 300
4	L.D.	F	40	6	Non compliance	8000	-	-
5	B.L.	F	44	48		157 000	< 600	< 23
6	P.E.	F	28	48		+	< 600	< 23
7	C.M.	F	47	48		766 000	60 100	178
8	C.A.	F	45	8	Complication after surgery	417 000	-	-
9	T.M.	M	26	16	Death of cerebral haemorrhage	> 1 000 000	< 600	-
10	P.C.	M	51	28	Non compliance	> 1 000 000	< 600	-

DISCUSSION

Many clinical trials have focused on the treatment of chronic hepatitis C patients on chronic haemodialysis with standard interferon, because ribavirin is not recommended. Some studies have used ribavirin at low doses (170-300 mg/d) together with standard interferon[23]. The results are encouraging but a careful monitoring of anaemia is mandatory. When anaemia occurs it is corrected with high doses of erythropoetin. On the other hand, post-transplant treatment of chronic C hepatitis with interferon is not recommended because it can induce graft rejection (15.4%-63.6% of cases)[24]. Also, post-transplant monotherapy with ribavirin or amantadine has been proven inefficient[24].

Fabrizi *et al*[6] have found a mean SVR of 37% and a mean dropout rate of 17% in chronic hepatitis C patients on dialysis after interferon monotherapy. Our experience in treatment of these patients with standard interferon showed that sustained biochemical response is 46.1% and sustained virological response (HCV-RNA) is 38.4% respectively 6 mo after interferon treatment[22].

The promising results of monotherapy with standard interferon in chronic haemodialysis patients with chronic hepatitis C[22,25-27], have shown that viral clearance occurs in 27%[27] to 64%[26] of patients after 12 mo of treatment with standard interfreon.

In patients on chronic haemodialysis, the combined treatment with interferon and ribavirin is difficult to manage because haemolysis is induced by ribavirin. There are studies in which ribavirin is administrated at low doses (170-300 mg/d), the results are remarkable but anaemia should be carefully monitored[23].

The second therapeutic option for patients on chronic haemodialysis with chronic C hepatitis is to use pegylated interferon. In most of the studies performed in patients with chronic C hepatitis and normal renal function, the response rate doubled when the patients switched from standard interferon to pegylated-interferon. Some 3 rd phase studies have been performed in Greece, Mexico, Great Britain and USA to evaluate the sustained virological response after treatment with pegylated interferon alpha 2a in patients on chronic haemodialysis.

Martin *et al*[28] demonstrated that the absorption, distribution and total clearance of pegylated-interferon alpha 2a (40 ku) are not very different from those in patients with normal renal function, and that the tolerability of pegylated-interferon alpha 2a and the adverse effects in patients on chronic haemodialysis are similar with those in patients without renal impairment. In our group the side effects were quite the same with those in "normal" patients with chronic hepatitis C treated with pegylated-interferon.

We reduced the dose of pegylated-interferon to 135 μg/wk in 2 cases (in one patient only for one month and in another until the end point of treatment). Various authors have recommended a dose of 180 or 135 μg/wk of pegylated-interferon alpha 2a in patients on chronic haemodialysis. We prefer to start with 180 μg/wk in order to reduce the dosage if severe side effects occur. We reduced the dosage in 2 patients due to thrombocytopenia and bleeding.

Data on the patients on haemodialysis treated with pegylated-interferon alpha 2b are rather discouraging. A study by Russo *et al*[29] on the HCV-infected patients on haemodialysis treated with pegylated-interferon alpha-2b showed that a poor tolerance is associated with substantial side effects. Also, a case report by Potthoff *et al*[30] showed that IFN-alpha 2b three times a week after haemodialysis seems to be better tolerated than pegylated-interferon-alpha 2b once a week. A randomized study performed by Mahmoud *et al*[31] in pretransplant haemodialysis patients with chronic hepatitis C treated with standard interferon alpha 2b, showed that IFN-treated patients have significantly better post-transplant hepatic functions and significantly lower rates of chronic allograft nephropathy. Further studies are needed to find out which type of interferon is better tolerated and has better results for the treatment of haemodialyzed patients with chronic hepatitis C.

Since there are more and more encouraging results of treatment with interferon in patients on chronic haemodialysis with chronic hepatitis C, it is likely that very soon all these patients can benefit from antiviral therapy (standard interferon alone or in combination with ribavirin, or pegylated-interferon).

After 12 wk of treatment with Peg-Interferon alpha 2a (40 ku) in patients on chronic haemodialysis with chronic C hepatitis, the early virological response (EVR) (HCV-RNA absent by PCR) was obtained in 87.5% (7/8) of the cases. All the patients that finished the 48 wk of treatment had normal transaminases (biochemical response) (6/6). We had to reduce the dose of Peg-Interferon in only 2 cases. Even if side effects occurred in most of the patients

(flue-like syndrome, thrombocytopenia or leucopoenia) they did not impose the discontinuation of treatment. The sustained virological response at 6 mo after the end of the therapy was achieved in 50% of the cases (3/6 patients) that finished the course of 48 wk of treatment.

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